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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,610	01/27/2004	Gregory J. LaRosa	1855.1052-029	3808

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EXAMINER	
BOESEN, AGNIESZKA	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,610	LAROSA ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *23-65* is/are withdrawn from consideration.

5)☐ Claim(s) *1,3-5,7,8,16,17,20 and 21* is/are allowed.

6)☒ Claim(s) *2,6,9-15,18,19 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *January 27, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received April 17, 2006.

Election/Restrictions

During a telephone conversation with Laurie Butler Lawrence on April 12, 2006 the restriction requirement of March 10, 2006 was discussed. Applicant traversed the restriction requirement and asked the Examiner if it was possible to rejoin groups I, II, and III together. Groups I, II, and III are drawn to the embodiment of nucleic acids encoding the heavy and light chains of an antibody, a fused gene and a host cell comprising the nucleic acids encoding the heavy and light chain of the antibody. Examiner agreed to rejoin groups I, II, and III together. Therefore, the restriction requirement between groups I, II and III is withdrawn.

Applicant's election of group I, II, and III in the response to the restriction requirement on April 17, 2006 has been acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement with respect to any other groups, the election has been treated as an election without traverse (MPEP § 818.03(a)). Upon further consideration claims 20 and 21, drawn to a method of preparing a humanized immunoglobulin have been rejoined. Thus, the restriction is deemed proper and is made FINAL.

Claims 1-22 are pending and under examination.

Priority

Acknowledgment is made for priority to a CIP application, 09/840,459, which is a continuation of PCT/US01/03537, which is a CIP of 09/497625, which is a CIP of 09/359193, which is a CIP of 09/121781. The limitations of the SEQ ID NO: 95 and SEQ ID NO: 96 are not seen in the applications of 09/497625, 09/359193, or 09/121781. As such the claims are granted the priority date of 2/2/01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 11, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 11, 22 and those dependent on claim 9, 11 and 22 are indefinite for reciting "portion of the heavy chain" because the exact meaning of the phrase is not clear. Is the "portion" the variable region of the heavy chain or is it a portion of the variable region itself?

Claims 2, 6, 13, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2, 6, 13, and 22 are indefinite for reciting the term "derived".

The term "derived" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the human framework region is to be derived to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derived" the human framework region is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

It is noted that a deposit for the 1D9 antibody would also be needed in this application. It is also unclear if a cell line which produces an antibody having the exact chemical identity of HF-21/28 and 4B4'CL are known and are publicly available, or can be reproducibly isolated without undue experimentation. Claims 2 and 6 recite the light chain of the

human HF-21/28 antibody and heavy chain of 4B4'CL and as such this encompasses not only the variable heavy chain but the constant heavy chain and as such the entire sequence is not disclosed in this application. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species 1D9, HF-21/28, and 4B4'CL. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or statement by an attorney of record over his or her signature and

registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years. Or 5 years after the last request for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Claims 2, and 10-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes SEQ ID NO: 95 and SEQ ID NO: 96 (page 40) as the sequences encoding the light and heavy chain of the antibody. The specification describes

framework region derived from a light and heavy chain of human origin derived from HF-21/28 and 4B4'CL antibody.

The instant specification provides insufficient description of the claimed genus of all antibodies having binding specificity for CCR2 and a genus of any framework region derived from a light and heavy chain of human origin.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the description regarding any other sequences, which encode for human light and heavy chain that have binding specificity for CCR2 and other antibodies from which the human framework region can be derived is lacking. Applicant has not demonstrated possession of the large genus of variants encompassed by claim 2 and 10-14. Accordingly, in the absence of insufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed structure of the

encompassed genus of genes encoding all CDRs having binding specificity for CCR2 and genes encoding all framework regions of human origin, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleotide sequence, SEQ ID NO: 95, encoding a light chain and SEQ ID NO: 96 encoding a heavy chain of the CDR, which is the variable region of the antibody, does not reasonably provide enablement for any nucleotide sequence encoding a CDR of a light and heavy chain that have binding specificity to CCR2. The specification, while being enabling for a framework region derived from a light and heavy chain of human origin derived from HF-21/28 and 4B4'CL antibody, does not reasonably provide enablement for any framework region derived from a light and heavy chain of human origin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The person of the ordinary skill in the art would require to do an undue experimentation to practice the invention as claimed.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the

predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an expression vector comprising a fused gene encoding a hunmanized immunoglobulin light chain and a heavy chain of a nonhuman antibody having binding specificity for CCR2 and a framework region derived from a light and heavy chain of human origin.

The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979, IDS # AW7). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the

claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody in unspecified order and fused to any human framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Scope of Enablement Rejection regarding host cell of claim 15, 18, and 19.

Claim 15, 18, and 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell, wherein the cell is isolated, purified or cultured, does not reasonably provide enablement for a host cell comprised within a living organism such as a transgenic animal or human. It is noted that the specification contemplates gene therapy in animals (pages 47). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The specification is not enabling for host cells comprised within either the human patient or the transgenic animal for the reasons set forth below.

(A) As drawn to gene therapy

The instant specification does not teach how to overcome problems with *in vivo* delivery and expression with respect to the administration of the claimed polynucleotides. The state of the art as of the priority date sought for the instant application is that *in vivo* gene delivery is not well developed and is highly unpredictable. For instance, Verma *et al.* (*Nature*, 1997, Vol. 389, pp. 239-242, herein, "Verma") teaches that the Achilles heel of gene therapy is gene delivery. Verma states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). As of the priority date sought, it was well known in the art how to infect or transfect cells *in vitro* or *ex vivo* with viral vectors. However, using viral vectors to deliver DNA to an organism *in vivo*, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism *in vivo* is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of *in vivo* systems. Orkin *et al.* states that clinical efficacy has not been definitively demonstrated with any gene therapy protocol ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995, herein, "Orkin", page 1, second paragraph). Orkin defines gene therapy as the transfer of DNA into recipient cells either *ex vivo* or *in vivo* (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to transfected cells located in a host. Orkin concludes that, "none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Until progress is made in these areas, slow and erratic success in applying gene transfer methods to patients can be expected". Orkin comments that direct administration of DNA or DNA in liposomes is not well developed and hindered by the

low efficiency of gene transfer (page 8, third full paragraph). Orkin teaches that adequate expression of the transferred genes is essential for therapy, but that in 1995, current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin states that in protocols not involving *ex vivo* infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies of the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma and Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

(B) as drawn to a transgenic animal

The specification states on page 47 that polynucleotides can be used to produce transgenic non-human animals. The specification does not provide guidance in the making of a transgenic animal comprising the instant polynucleotides in the transformed cells. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, *Journal of Biotechnology*, 1994, 34:269-287), see bridging paragraph of pages 272-273. Expression is heavily dependent on the site of integration in the host genome and the site of integration is

presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would undergo undue experimentation in order to make a transgenic animal comprising the claimed host cells.

Amendment of claims 15, 18, and 19 to recite "isolated host cell" would overcome this rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AB

Agnieszka Boesen, Ph.D.
Examiner
June 16, 2006

Stacy B. Chen 6/16/06

Stacy B. Chen
Primary Examiner